REMARKS

Claims 1, 23-36 and 49 are pending in the subject application. Claims 33 and 49 have been amended. No new matter has been added.

Applicants note with gratitude the Examiner's removal of the 35 U.S.C. § 112, ¶ 2 and prior art rejections previously asserted in the Office Action of September 21, 2004.

Applicants also note with gratitude the multiple telephonic conferences held with Examiner Audet on April 13 and 29 which clarified the Examiner's election requirement. As an initial matter, the *Office Action* appeared to require that Applicants amend the claims "to be drawn to the elected invention monomer A to be TKPPR only" or else the Response will "be nonresponsive." (*Office Action*, p. 3). In the telephone conference of April 13, the Examiner confirmed, irrespective of the *Office Action*'s statement, that failure to amend the claims in the present *Response* will not be considered nonresponsive, and will not result in abandonment of the present application.

During the same conference, Applicants reiterated their position that Applicants never elected TKPPR monomer only. Rather, Applicants maintain that they have always elected the monomer of TKPPR or analogues thereof. *Amendment* of June 25, 2004, p. 9. Applicants also reiterated that they know of no authority by which the claims must be narrowed in the manner required in the *Office Action.* The Examiner stated that the sole reason for justifying this requirement is that he is unable to do a comprehensive search for all monomers of TKPPR analogues. Applicants disagreed, *inter alia*, noting that the claimed limitation recites a more narrow subclass of TKPPR analogues and further that the most relevant search for prior art would be with the term TKPPR (instead of TKPPR analogues, which would be cumulative since analogues are derived from TKPPR). After further clarification of Applicants' position, the

Examiner agreed to withdraw this amendment requirement provided Applicants expressly agree to the condition that any search which yields a reference (or a proper combination of references) containing all of the recited A, L and B elements of a respective claim would render that respective claim unpatentable, irrespective of whether A in that appropriate reference is disclosed as a "monomer of TKPPR" or as a "monomer of a TKPPR analogue which specifically binds to NP-1 or cells that express NP-1 with avidity that is equal to or greater than TKPPR." Applicants hereby agree to such condition to facilitate removal of this amendment requirement.

The Examiner further requested Applicants disclose a smallest "core" of the monomer of TKPPR analogue to further assist the Examiner's search efforts. As explained previously, a monomer of a TKPPR analogue is a structural derivative of a parent compound that often differs from it by a single element (*The American Heritage Dictionary of the English Language*, 4th Ed. 2000). Searching TKPPR itself should be sufficient to yield art regarding analogues of TKPPR, where as here the analogues must have the biological activity of TKPPR (*e.g.*, bind to the NP-1 receptor with equal or greater affinity).

I. Claims 1, 23-36 and 49 Satisfy 35 U.S.C. § 112, ¶ 1

Claims 1, 23-36 and 49 have been rejected under 35 U.S.C. § 112, ¶ 1, as purportedly lacking enablement for a TKPPR analogue as monomer A. Applicants respectfully traversed this rejection in its Response of December 21, 2004. However, the *Office Action* did not address Applicants' Response, stating only that "Applicants' arguments are moot and have not been considered." Because this rejection appeared to have been maintained without addressing the merits of Applicants previous arguments, Applicants summarize those arguments below in the interest of completeness and respectfully request the withdrawal of this rejection.

Moreover, to further confirm that the recited limitation "a monomer of a TKPPR analogue which specifically binds to NP-1 cells or cells that express NP-1 with avidity that is equal to or greater than TKPPR" is fully enabled by the present specification, Applicants submit herewith the Declaration of Mathew von Wronski, PhD ("*von Wronski Declaration*"), who is a co-inventor of this invention, for the Examiner's consideration and for entering into the record.

As an initial matter, the basis for this rejection is unclear. Specifically, as the *Office Action* admits, the Specification is enabling for practicing the claimed invention with A as a monomer of TKPPR. Therefore, it conclusively follows that the Specification is also enabling for practicing the claimed invention with A as a monomer of a TKPPR analogue since the chemistry of analogues are well understood by one of ordinary skill in the art. *von Wronski Declaration*, ¶¶ 13-15. Moreover, the recited limitation, "a monomer of a TKPPR analogue *that specifically binds to NP-1 cells or cells that express NP-1 with avidity that is equal to or greater than TKPPR,*" is narrower than that quoted by the Examiner and is fully enabled. *von Wronski Declaration*, ¶¶ 16-18.

Furthermore, confirmation of this conclusion is supported by the thousands of U.S. Patents issued by the USPTO in the chemical, biological and pharmaceutical classes which contain the term "analogue" or "analog" in the claims. This is compelling evidence that the term "analogue" satisfies 35 U.S.C. § 112, ¶ 1.

Applicants note that the standard for determining whether the specification meets the enablement requirement is whether the experimentation needed to practice the invention is undue. MPEP 2164.01. Applicants submit that the answer is No. Specifically, one of ordinary skill in the art would be able to practice the claimed invention without undue experimentation wherein A is a monomer of a TKPPR analogue that specifically binds to NP-1 cells or cells that

express NP-1 with avidity that is equal to or greater than TKPPR. *von Wronski Declaration*, ¶¶ 17 and 18. A review of the eight (8) *Wands* factors confirms this conclusion:

1. Breadth of the claims

Claims 1, 23-32, 34-36 and 49 are limited to compositions wherein, *inter alia*, A is a monomer of TKPPR or a monomer of a TKPPR analogue that specifically binds to NP-1 cells or cells that express NP-1 with avidity that is equal to or greater than TKPPR. Applicants note that this is a much narrower limitation than simply "a TKPPR analogue."

2. Nature Of The Invention

Claims 1, 23-32, 34-36 and 49 are directed to compositions of the formula A-L-B wherein, *inter alia*, A is a monomer of TKPPR or a monomer of a TKPPR analogue that specifically binds to NP-1 cells or cells that express NP-1 with avidity that is equal to or greater than TKPPR.

3. The State Of The Prior Art

In the pharmaceutical, chemical, and biological field, it is well known and understood that a reference enabling the use of a parent compound would enable one of ordinary skill in the art to practice the claimed invention with an analogue of the parent compound. *von Wronski Declaration*, ¶¶ 14 and 15. The USPTO has confirmed this conclusion by issuing thousands of patents in the pharmaceutical, chemical and biological classes with the term "analogue" or "analog" in the claims.

4. The Level Of One Of Ordinary Skill

A person skilled in the art would be a scientist with an undergraduate degree in chemistry or biochemistry and at least two years of post graduate research experience in the field of diagnostic and therapeutic agents.

5. The Level Of Predictability In The Art

As the chemistry of analogues or analogs is well understood, there exists a level of predictability in the art between parent compounds and their analogues. *von Wronski Declaration*, ¶ 15.

6. The Amount Of Direction Provided

The present Specification, as the *Office Action* admits, is enabling for the claimed invention wherein A is a monomer of TKPPR.

The Specification further teaches TKPPR analogues that are useful in the present invention have specific characteristics – for example, they include molecules that target the NP-1 VEGF binding receptor with avidity that is greater than or equal to TKPPR (Specification, pages 10-11). Examples of acceptable TKPPR analogues are listed throughout the Specification, *e.g.*, at page 11, lines 25-30. The Specification lists examples of TKPPR analogues that result from, *e.g.*, amino acid substitutions, "made with synonymous groups" (page 11, lines 3-9. Indeed, the Specification even provides specific amino acids which may be substituted for each of the Thr, Lys, Pro and Arg residues in TKPPR. *See* Table, page 11. Furthermore, the Specification teaches that TKPPR analogues may be prepared from deletions or insertions of amino acids in the TKPPR sequence or from muteins of the TKPPR sequence (page 10, lines 20-26) as well as from

peptidomimetics or pseudopeptides incorporating changes to the amide bonds of the peptide backbone (page 11, lines 18-19). Thus, the Specification provides ample guidance on practicing the claimed invention, both when A is a monomer of TKPPR and when A is a monomer of a TKPPR analogue that specifically binds to NP-1 cells or cells that express NP-1 with avidity that is equal to or greater than TKPPR. *von Wronski Declaration*, ¶ 16.

7. The Existence Of Working Examples

No examples need to be provided in order to establish that the invention is enabled. MPEP § 2164.02 ("Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed"). This is especially true where the present Specification discloses the invention in such a manner that one skilled in the art will be able to practice the claimed invention with A as a TKPPR monomer without any undue experimentation. *von Wronski Declaration*, ¶ 17. Nevertheless, the Specification does provide specific working examples with TKPPR analogues, *e.g.*, GTKPPR (Examples 4, 14, etc.).

8. The Quantity Of Experimentation Needed

The quantity of experimentation needed, if any, would not be undue. First, the claim limitation at issue is a narrow limitation, and not one directed to all TKPPR analogues as the *Office Action* asserts. (Factors 1-2, *supra*). Second, one of ordinary skill in the art with the prerequisite education and work experience would understand the chemistry of analogues, for which the state of technology is well known in the art. (Factors 3-5, *supra*). Third, the present Specification both discloses and provides working examples of using TKPPR analogues. (Factors 6-

7, *supra*). Therefore, for all of these reasons, one of ordinary skill in the art would be able to practice the claimed invention without undue experimentation. *von Wronski Declaration*, ¶¶ 13-18.

As such, Applicants respectfully submit that the Specification is enabled for the pending claims and request that the rejection of claims 1, 23-36 and 49 under 35 U.S.C. § 112, ¶ 1 be reconsidered and withdrawn.

Applicants further note that claim 33 does not include the subject term "a TKPPR analogue" and thus should not have been included with this ground for rejection. Applicants reiterate their request for correction of the instant status for claim 33.

II. Claims 1, 23-36 and 49 Are Patentable Over Barbera-Guillem In View of Pollak

Claims 1, 23-36 and 49 have been further rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 6,333,110 to Barbera-Guillem ("Barbera-Guillem") in view of U.S. Patent No. 5,789,555 to Pollak ("Pollak"). For the reasons set forth below, Applicants traverse each of these rejections.

In order to establish a *prima facie* case of obviousness, three factors must be shown: (1) there must be some suggestion or motivation to modify the reference or combine reference teachings; (2) there must be a reasonable expectation of success in the combination; and (3) the prior art reference or references must teach or suggest all of the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); MPEP §§ 2142 and 2143. Applicants respectfully submit that a *prima facie* case of obviousness cannot be established since none of these three factors have been met.

1. There Is No Proper Motivation Or Suggestion To Combine

a. There Is No Motivation Or Suggestion To Combine The References

Barbera-Guillem is directed to functionalized nanocrystals as imaging agents, and methods for fluorescence imaging of tissues labeled with such nanocrystals (Barbera-Guillem, col. 1, lines 14-20). On the other hand, Pollak is directed to compositions and processes useful for generating metal-ligand complexes or metal-labeled compounds useful as imaging agents. (Pollak, col. 1, lines 3-6). There is no suggestion or motivation in the art to combine a reference directed to functionalized nanocrystals as fluorescence imaging agents with a reference directed to a metal imaging agent.

b. There Is No Motivation Or Suggestion To Make The Claimed Invention

Furthermore, for the sake of argument, even if combining the asserted references were permissible (Applicants maintain they are not), there is also no motivation or suggestion to combine the teachings of Barbera-Guillem and Pollak in the manner asserted by the *Office Action* to arrive at the presently claimed invention.

The *Office Action* asserted that Barbera-Guillem teaches imaging agents using [A] peptides as targeting molecules, [L] linkers and [B] substrates (*i.e.*, the actual target) such as phospholipids. The *Office Action* then stated that it would "have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use the targeting peptide TKPPR as the peptide of Barbera-Guillem, because Pollak teaches the advantageous use of the targeting peptide of TKPPR for tissue targeting in imaging agent composition."

This assertion is incorrect because one of ordinary skill in the art would know that TKPPR (*i.e.*, the targeting molecule in this asserted combination) does not target phospholipids (*i.e.*, the targeted substrate in this asserted combination). As such, one of ordinary skill in the art

would not be motivated to make this asserted combination of elements, and the asserted combination of elements could only have been arrived at with the use of impermissible hindsight from Applicants' specification and claims. *Grain Processing Corp. v. American Maize-Products Co.*, 840 F.2d 902, 907, 5 USPQ2d 1788, 1792 (Fed. Cir. 1988) ("Care must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.'"); *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."); MPEP 2142. Thus, withdrawal of this rejection is respectfully requested.

c. The Proposed Modification Would Impermissibly Render The Asserted Art Unsatisfactory For Its Intended Purpose

The configuration of Barbera-Guillem's compound is as follows:

[quantum dot]–[capping compound]–[diaminocarboxylic acid layer]–[affinity ligand]

Col. 3, lines 31-40; Figs 1-2, claim 1. The affinity ligand would then bind to the targeted substrate in a living being in order to permit imaging of the tissue. Col. 4, lines 48-51, 60-64. Thus, the configuration of Barbera-Guillem's compound once attached to the targeted substrate in the living being becomes:

[quantum dot]–[capping compound]–[diaminocarboxylic acid layer]–[affinity ligand]-[substrate]

The proposed modification which uses TKPPR as the targeting molecule (*i.e.*, affinity ligand) on Barbera-Guillem's compound would not result in Barbera-Guillem's compound targeting phospholipids (*i.e.*, the targeted substrate). As such, it would render the Barbera-

Guillem compound unsatisfactory for its intended purpose, which in the asserted combination would be to target phospholipids. As such, withdrawal of this rejection is respectfully requested.

d. The Proposed Modification Impermissibly Changes The Principle Of Operation Of The Asserted Reference

Not only would the use of TKPPR as the peptide in the Barbera-Guillem compound impermissibly render Barbera-Guillem's invention unsatisfactory for its intended purpose, but it would also impermissibly change the principle of operation for Barbera-Guillem's invention since Barbera-Guillem's compound would not target phospholipid substrates. Thus, for the same reason as discussed in the preceding paragraph, the asserted combination is improper.

As such, there is no motivation or suggestion to combine Pollak with Barbera-Guillem, and withdrawal of this rejection is respectfully requested.

2. There Is No Reasonable Expectation Of Success

There is further no reasonable expectation of success in combining the teachings of the Pollak and Barbera-Guillem. *In re Vaeck,* 947 F.2d 488, 20 U.S.P.Q.2d 1438, 1442 (Fed.Cir. 1991). Both the motivation to combine and the reasonable expectation of success must be found in the prior art and not Applicants' disclosure. *Id.* 20 U.S.P.Q.2d at 1442.

As explained in the preceding section, there is no reasonable expectation of success based on the teachings of Pollak and Barbera-Guillem that the use of TKPPR as taught by Pollak as the affinity ligand in the invention of Barbera-Guillem would be successful in targeting phospholipids substrates since TKPPR does not target phospholipids. No evidence has been provided to the contrary.

Therefore, for this additional reason, Applicants respectfully submit that it is improper to combine the Pollak and Barbera-Guillem references, and withdrawal of this rejection is respectfully requested.

3. The Asserted Reference Combination Fails To Teach All Limitations

In addition to lacking a motivation to combine and a reasonable expectation of success, the references, even if combined, still fail to teach all of Applicants' claimed limitations.

Independent claims 1, 29 and 49 each recite a compound with the formula A-L-B (*e.g.*, a linker (L) connecting the TKPPR monomer or a monomer of a TKPPR analogue (A) which specifically binds to NP-1 or cells that express NP-1 with avidity that is equal to or greater than TKPPR, to the phospholipid (B)).

However, the proposed modification would have the following configuration:

> *[quantum dot]–[capping compound]–[diaminocarboxylic acid layer]–[TKPPR]-[phospholipid substrate*]

Thus, at the very minimum, this asserted combination is missing a linker [L] to connect the TKPPR with the phospholipid. As such, the asserted combination fails to teach each element of Applicants' claims and withdrawal of this rejection is respectfully requested.

Applicants note that the specific compounds recited in claim 33 are also not taught or suggested in any combination of Pollak and Barbera-Guillem. Therefore, in the event that the 35 U.S.C. § 103 rejection is not withdrawn in its entirety, the rejection of claim 33 should be withdrawn for this additional basis.

CONCLUSION

In view of the preceding remarks, Applicants maintain that the claims are now in condition for allowance, early notice of which is earnestly sought.

No fee(s) are believed to be due in connection with the filing of this *Response*. If there are any such fees, The Director is hereby authorized to charge any fees due or credit any overpayment to Deposit Account No. 50-0540.

If there are any outstanding issues the Examiner is respectfully invited to contact Applicants' undersigned attorneys to resolve them.

Respectfully submitted,

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